



Treatment for meibomian gland dysfunction and dry eye symptoms with a single-dose vectored thermal pulsation: a review

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Purpose of review

Meibomian gland dysfunction (MGD) is understood to be a highly prevalent, chronic progressive disease and the leading cause of dry eye. All available published peer-reviewed results of the novel vectored thermal pulsation therapy for patients with MGD are investigated.

Recent findings

The PubMed and meeting abstract search revealed a total of 31 peer-reviewed reports on vectored thermal pulsation therapy at the time of the search (eight manuscripts and 23 meeting abstracts). All manuscripts evidence a significant increase in meibomian gland function (~3×) and symptom improvement post a single 12-min treatment. Additional reported objective measures such as osmolarity, tear break-up time, or lipid layer thickness also increased as a result of the therapy; however, not all findings were statistically significant. The randomized controlled studies evidence sustained gland function and symptom relief lasting out to 12 months. The uncontrolled case series evidence significantly longer duration of effect.

Summary

A single 12 minute vectored thermal pulsation treatment allows for reducing dry eye symptoms, improving meibomian gland function and other correlates of the ocular surface health.

Keywords

dry eye disease, meibomian gland dysfunction, ocular surface disease

INTRODUCTION

The definition of 'dry eye' continues to evolve. Despite this evolution, it is well understood to be a multifactorial disease state that afflicts many millions of people worldwide [1]. Historically, dry eye has been understood to be predominately due to insufficient aqueous production [2], and the vast majority of our diagnostics and therapeutics have remained largely focused on aqueous replacement and production [1]. Conversely, recent advances have lead to the conclusion that meibomian gland dysfunction (MGD) is likely the leading cause of all dry eye [3,4]. This conclusion is supported by a large body of evidence-based medicine reporting that compromise to the lipid layer negatively impacts all aspects of ocular surface health [3–5,6^{***},7–9].

The awareness that ocular surface health cannot be sustained in the absence of a healthy lipid layer has resulted in a resurgence of interest in meibomian gland function [3,4]. Over the last decade, there have

been multiple new developments in diagnostic evaluation of gland function as well as therapeutic interventions for MGD [10–13]. The focus of this review is the reported efficacy of vectored thermal pulsation therapy designed to treat MGD [11].

It has been known for over 150 years that treatment for MGD/obstruction to be optimally effective the stagnated contents of the glands must be evacuated [14–17]. Until recently, the only known method to evacuate stagnated gland contents has been to manually express the glands using physical

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KEY POINTS

- Evacuation of stagnated gland contents remains the necessary core therapy for rehabilitating gland function and reducing symptoms of eye dryness in patients with MGD.
- MGD is understood to be the leading cause of dry eye, in part, because one cannot achieve ocular surface health and wellness in the absence of a healthy lipid layer and tear film stability.
- Successful ocular surface dryness management requires a shift in focus from tear production and quantity to measures of meibomian gland function and tear film stability.
- No other single-dose therapy offers the same efficacy profile for reducing dry eye symptoms, improving meibomian gland function and other correlates of the ocular surface health, as well as vectored thermal pulsation for the evacuation of stagnated gland contents.

force. This procedure although effective is also extremely uncomfortable. In fact, it has been reported that the primary limitation to efficacy of manual expression is pain [18].

A long-standing adjunctive therapy for MGD has been warm compresses [19]. Warm compresses do not evacuate stagnated gland contents but, if appropriately administered, they have the ability to warm the gland contents [20] and do offer some therapeutic value [21,22]. Unfortunately, there is no standard warm compress method but even if one existed, the limitations and safety concerns of heating the external lid surface with the intent of heating the meibomian glands cannot be overcome with even the most optimal warm compress technique [23,24].

The obstacles to efficient heat transfer from the outer to the inner lid surface, imposed by the lid tissue and blood flow, have been discussed elsewhere [11,17,20]. Vectored thermal pulsation therapy was designed to bypass these obstacles and simultaneously evacuate the gland contents while heating the glands to therapeutic levels, at least 40°C [5,20]. Full description of the device has been reported previously [11,17] but briefly, the LipiFlow (TearScience Inc., Morrisville, NC, USA) applies heat (42.5°C) to both inner eyelid surfaces whereas pulsating pressure is simultaneously applied to the outer eyelids using an inflatable air bladder. This temperature allows for effective heating of the meibomian gland contents [5,25,26] while operating within a well tolerated zone so as not to cause thermal injury [27,28]. As such, the LipiFlow is capable of evacuating meibomian glands of the upper and lower eyelids simultaneously [11,17,29].

The combination of efficient and safe heat transfer to the glands with simultaneously evacuation pressure to milk the glands of their contents, resulted in a vast reduction in required pressure (20–30 pounds per square inch (PSI) with manual expression vs. six PSI with the vectored thermal pulsation [17,18]). Hence, in contrast to the predictably painful experience of manual expression, there are no published or anecdotal reports of pain during vectored thermal pulsation therapy with the LipiFlow. Furthermore, since the upper and lower lids can be simultaneously and comprehensively treated, the single 12-min therapy has been surprisingly effective [17,30,31,32^{***},33^{***}].

LipiFlow received US Food and Drug Administration clearance based on its open-label, randomized, controlled, multicenter trial compared with warm compress therapy for the treatment of MGD [17]. There have been a number of subsequent studies that have demonstrated the efficacy and safety of LipiFlow treatment in treating MGD. The purpose of this review is to examine the reports on vectored thermal pulsation therapy for MGD in the peer-reviewed literature.

METHODS

Using PUBMED in January 2015 (no time limits), eight related publications were found. Additionally, related American Society of Cataract and Refractive Surgery, European Society of Cataract and Refractive Surgery, Association for Research in Vision and Ophthalmology, European Association for Vision and Eye Research, and American Academy of Ophthalmology abstracts were searched and included in the review. In total, 31 articles/abstracts (five clinical trials, three case reports, and 23 meeting abstracts) were included in the study. In this review, we systematically examined the literature documenting the outcomes of single 12-min treatment of LipiFlow thermal pulsation system on MGD-associated evaporative dry eye.

RESULTS

Review of efficacy outcomes

Meibomian gland function

The literature review indicates that the LipiFlow thermal pulsation device is effective in restoring the meibomian gland function, see Tables 1 and 2.

Interpretation of the meibomian gland function scoring

In the original safety and efficacy trial, a meibomian gland secretion scoring system was developed to

Table 1. Review of LipiFlow literature (peer-reviewed publications) reporting efficacy outcomes: meibomian gland function, symptom scores, tear break-up time, and lipid layer thickness

Author/Study	Type of study	Patients (eyes)	Last follow-up	Meibomian gland function, MGE (MGYLS)		SPEED (OSDI)		TBUT (s)		LLT/ICU average	
				Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Finis <i>et al.</i> [38***]	Prospective randomized clinical trial	26 (52)	6 months	2.9 ± 1.6	6.4 ± 4.6 ^a	16 ± 7 (42 ± 19)	12 ± 7 ^a (33 ± 21) ^a	9.5 ± 8.7	10.0 ± 6.7	44.0 ± 15.6	51.3 ± 20.4 ^a
Finis <i>et al.</i> [36]	Prospective randomized clinical trial	17 (34)	3 months	2.5 ± 1.4	5.5 ± 3.6 ^a	16.8 ± 5.6 (46.2 ± 14.8)	14.5 ± 7.2 (34.6 ± 19.6) ^a	7.9 ± 8.5	9.9 ± 7.0	43.4 ± 9.9	47.4 ± 16.7
Greiner [31]	Retrospective observational case series	18 (36)	1 year	4.0 ± 3.4	7.3 ± 4.6 ^a	12.9 ± 3.8 (22.2 ± 14.2)	6.3 ± 5.5 ^a (12.4 ± 14.6) ^a	4.9 ± 3.0	6.0 ± 4.4 ^a		
Korb and BlackieCase [49]	Case report	1 (2)	7 months	(OD-1, OS-1)	(OD-4, OS-4)	OD-24.0, OS-28.0	OD-6, OS-6	OD-4, OS-4	OD-7, OS-9		
Greiner [30]	Clinical trial	21 (42)	9 months	4.4 ± 4.0	11.7 ± 5.9 ^a	12.9 ± 4.0 (23.4 ± 14.4)	6.2 ± 7.1 ^a (12.4 ± 15.3) ^a	4.8 ± 3.2	7.1 ± 5.6 ^a		
Lane <i>et al.</i> [17]	Prospective, randomized, multicenter clinical trial	69 (138)	4 weeks	6.3 ± 3.5	16.7 ± 8.7 ^a	14.3 ± 4.8 (32.0 ± 20.0)	7.6 ± 5.8 ^a (16.6 ± 18.1) ^a	5.5 ± 2.9	7.4 ± 5.5 ^a		
Friedland <i>et al.</i> [29]	Prospective multicenter clinical trial	7 (14)	3 months	3.4 ± 3.2 (2.9 ± 2.8)	9.9 ± 3.2 ^a (9.9 ± 3.1) ^a	16.2 ± 5.4 (37.0 ± 23.8)	7.8 ± 4.8 ^a (18.3 ± 14.0) ^a	5.2 ± 2.6	11.0 ± 6.3 ^a		
Korb and BlackieCase [11]	Case report	1 (2)	3 months	(OD-0, OS-1)	(OD-6, OS-6)	OD-20.0, OS-19.0 (OD-70.8, OS-66.7)	OD-3, OS-4 (OD-18.8, OS-14.6)	OD-5.2, OS-4.5	OD-10.7, OS-13.8		

ICU, interferometric color unit; LLT, lipid layer thickness; MGE, meibomian gland expression; MGYLS, meibomian glands yielding liquid secretion; OSDI, Ocular Surface Disease Index; SPEED, standard patient evaluation of eye dryness; TBUT, tear break-up time.

^aSignificant.

Table 2. Review of LipiFlow literature (meeting abstracts) reporting efficacy outcomes: meibomian gland function, symptom scores, tear break-up time, and lipid layer thickness

Author/ Study	Type of study	Patients (eyes)	Last follow-up	Meibomian gland function, MGE (MGYLS)		SPEED (OSDI)		TBUT (s)		LLT/ICU average	
				Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Bowden [34]	Retrospective single center	62 (119)	6–8 weeks	10.8 ± 6.2	15.4 ± 5.0 ^a	10.5 ± 7.4	4.9 ± 4.0 ^a	67.8 ± 24.1	73.2 ± 22.4 ^a		
Epitropoulos [35]	Retrospective case series	51 (82)	6–8 weeks	3.0 ± 3.3	14.0 ± 8.9 ^a	16.0 ± 7.3	11.0 ± 6.1 ^a	4.0 ± 3.4	7.3 ± 4.3 ^a		
Greiner [42]	Prospective, multicenter, open-label, randomized clinical trial	188 eyes	12 months	6.2 ± 3.7	17.3 ± 9.1 ^a	(45.6 ± 21.1)	(21.6 ± 21.3) ^a				
Holland [32 ^a]	Prospective, multicenter, open-label clinical trial	99 (197)	12 months	6.3 ± 3.7	17.3 ± 9.1 ^a						
Jackson 2015	Prospective, multicenter, open-label, randomized clinical trial	16 (32)	3 months	8.3 ± 3.3	20.9 ± 9.8 ^a						
Kusa and Piorella [56]	Retrospective case series	33 (64)	2 years					52.1 ± 19.5	91.8 ± 14.6		
Majumdar [33 ^a]	Prospective, multicenter, open-label clinical trial	200 (400)	1 year	6.4 ± 3.7	17.3 ± 9.1 ^a	(44.1 ± 20.4)	(21.6 ± 21.3) ^a				
Einan-Lifshitz <i>et al.</i> [57]	Retrospective case series	19 (30)	1 month		(No significant change)		Significant improvement in dry eye symptoms in 42.11% (8) patients	No significant change	No significant change		
Finis <i>et al.</i> [36]	Prospective, randomized, crossover, observer-masked trial	31	3 months		Significant improvement		Significant reduction in subjective symptoms				
Greiner [39]	Prospective, randomized, crossover, multicenter clinical study		3 years	4.4 ± 4.0	18.4 ± 6.2 ^a						
Kaercher [52]	Retrospective case series	10	4 weeks			(54.3 ± 21.3)	(51.2 ± 27.5)	11.8 ± 3.4	15.6 ± 7.9 ^a		

Table 2 (Continued)

Author/ Study	Type of study	Patients (eyes)	Last follow-up	Meibomian gland func- tion, MGE (MGYLS)		SPEED (OSDI)		TBUT (s)		LLT/ICU average	
				Pretreat- ment	Posttreat- ment	Pretreat- ment	Posttreat- ment	Pretreat- ment	Posttreat- ment	Pretreat- ment	Posttreat- ment
Peizold and Bedi [50]	Case report	1 (2)	18 months	(OD-8, OS-10)	(OD-12, OS-13)	20	12	<5 in both the eyes	OD-33 ± 5, OS-31 ± 5	OD-77 ± 5, OS-70 ± 2	
Rooney <i>et al.</i> 2014	Hospital-based, longitudinal, interventional study	25	3 months	4.8 ± 0.5	8.3 ± 1.0 ^a	(45.0 ± 0.9)	(28.1 ± 11.5) ^a	2.5 ± 0.5	3.5 ± 1.0		
Schallhorn <i>et al.</i> [46**]	Retrospective case series	91 (169)	5–141 months ^b	OD-4.4 ± 2.0, OS-4.8 ± 2.1	OD-17.6 ± 7.6	15 ± 5	9.4 ± 5.1 ^a		9.4 ± 5.1 ^a	OD-68.2 ± 23.4, OS-70.6 ± 22.6	
Sattjowatcharaphong <i>et al.</i> [45**]	Retrospective case series	23 (34)	6–10 weeks	7 ± 5	19 ± 9 ^a	15 ± 5	9 ± 4 ^a		9 ± 4 ^a	No significant change	
Greiner [41]	Prospective case series	17	4 years	4.5 ± 3.6	17.2 ± 5.4 ^a	13.7 ± 4.3	10.6 ± 6.8 ^a (returned to BL at 2 years)		10.6 ± 6.8 ^a	Returned to BL at 1 year	
Michee <i>et al.</i> [44]	Prospective case series	17 (20)	1 month	2.8 ± 1.1	6.8 ± 2.3 ^a	15.4 ± 4.9, (22 ± 8.4)	12.7 ± 5.8 ^a , (21.7 ± 9.5)	3.1 ± 1.6	5.8 ± 2.5 ^a	57.3 ± 21.8 62.5 ± 23	
Greiner [40]	Prospective case series	18	3 years	4.8 ± 3.7	11.4 ± 4.6 ^a	13.1 ± 4.6	6.2 ± 5.5 ^a	4.1 ± 1.9	6.2 ± 5.5 ^a	Returned to BL at 1 year	
Kim <i>et al.</i> [48]	Retrospective case series	8 (8)	12 months	(1.1 ± 0.8)	(3.1 ± 0.6)						
Korb and Blackie [51]	Prospective case series	12	1 month	4.5 ± 3.0	18.1 ± 8.1 ^a	17.4 ± 4.5	11.9 ± 5.3 ^a		11.9 ± 5.3 ^a		
Greiner [47]	Prospective, open-label, randomized, multicenter clinical trial	69	4 weeks	6.2 ± 3.6 (0.6 ± 0.9)	16.7 ± 8.7 ^a , (2.6 ± 3.6) ^a						
Majumdar <i>et al.</i> 2010	Prospective, open-label, randomized, crossover multicenter clinical trial	69	4 weeks	6.3 ± 3.5	16.7 ± 8.7 ^a			5.5 ± 2.9	7.4 ± 5.5 ^a		

BL, base line; ICU, interferometric color unit; LLT, lipid layer thickness; MGE, meibomian gland expression; MGYLS, meibomian glands yielding liquid secretion; OSDI, Ocular Surface Disease Index; SPEED, Standard Patient Evaluation of Eye Dryness; TBUT, tear break-up time.
^aSignificant.
^bAverage: 43.8 ± 23.0 months.

assess the meibomian gland function [17]. A total of 15 glands were evaluated along the lower eyelid margin, consisting of five glands located in each of the temporal, central, and nasal regions. For each of the 15 glands, expressed secretion characteristics were graded on a scale of 3 (clear liquid secretion), 2 (cloudy liquid secretion), 1 (inspissated/toothpaste consistency), and 0 (no secretion). However, for quicker clinical assessment, the number of meibomian glands yielding any liquid secretions was also recorded. In the subsequent studies, most of the authors have retained the meibomian gland expression (MGE) scoring method as reported by Lane *et al.* [17,30,31,32¹¹,33¹¹,34–37,38¹¹,39–44,45¹¹,46¹¹,47–49]. However, several studies have used the simpler method of counting the number of functional glands, that is, meibomian glands yielding liquid secretion (MGYLS) [29,50–54]. The pretreatment MGE and MGYLS scores have been found to be in the range of 2.9–6.3 and 1.1–2.9, respectively. These values reflect a variation in severity of the disease of the patients in various studies. Nevertheless, all studies to date have demonstrated a significant rise in both MGE score (posttreatment range 5.5–20.9 and number of MGYLS (posttreatment range 4–13) [29,50–54].

Symptom scores

Either one or both of the two validated dry eye questionnaires was reported in all of the peer-reviewed studies and abstracts: the standard patient evaluation of eye dryness [55] or the Ocular Surface Disease Index [56] or both. All studies, except one, have reported a statistically significant decrease in mean symptom scores after LipiFlow treatment from baseline. Regardless of the short or long-term follow-up, a significant drop in symptom scores has been reported with pretreatment standard patient evaluation of eye dryness and OSDI scores ranging between 12.9 to 28.0 and 22.2 to 70.8, respectively, to posttreatment values ranging between 6.2 to 14.5 and 12.4 to 51.2, respectively [30,31,32¹¹,33¹¹,34–37,38¹¹,41,45¹¹,50]. The studies with follow-up durations between 1 and 4 years document that the improvement in symptom scores following single LipiFlow treatment could be maintained surprisingly long periods of up to 4 years [33¹¹,38¹¹,39–41,46¹¹,50,58]. In the one study that did not find statistical significant improvement in symptom score, the LipiFlow treatment was done in patients with chronic dry eye with duration ranging from at least 5 years to more than 10 years [58]. In this study, although the patients did show improvement after 4 weeks of the treatment, the improvement in OSDI score was not statistically significant. These results

were hypothesized to be possibly due to dysfunctional pain nociceptors, associated with long-lasting dry eye [58–62].

Other signs of dry eye

In general, lipid layer thickness (LLT) has been found to be thinner in patients with obstructive MGD than normal eyes [61]. Furthermore, LLT has also been found to be negatively correlated with upper and lower meibomian gland loss in patients with obstructive MGD [61]. Available literature has documented a pretreatment LLT between 31.0 and 67.8 interferometric color unit per nanometer, which significantly improved to a range of 47.4–91 interferometric color unit per nanometer post-LipiFlow treatment [34,36,38¹¹,44,46¹¹,52,62].

As thicker LLT is associated with better tear film stability, improved tear break-up time (TBUT) is expected as a result of LLT rise. Pretreatment TBUT has been reported to range between 4.0 and 11.8 s in the available literature, which improved to values ranging between 7.3 and 15.6 s post-LipiFlow treatment [11,17,29,30,31,36,38¹¹,40,52,58]. Furthermore, an inverse correlation between LLT and tear osmolarity has been documented [36]. Finis *et al.* and Kaercher [37,58] studied tear osmolarity in patients who underwent single LipiFlow treatment. The results demonstrated improvement in osmolarity; however, it was not statistically significant in either study. Others reports have shown significant improvement in corneal surface staining and tear osmolarity [17,29,36,38¹¹,52,58].

Review of safety parameters

The LipiFlow device is designed to safely and comfortably vault the cornea, applying controlled heat to the glands while protecting the surfaces both in proximity of and in contact with the device. None of the studies reported any unanticipated or serious device-related adverse events during treatment or follow-up. In particular, Lane *et al.* [17] found the mean discomfort score during LipiFlow treatment to be 1.4 on a scale of 0–10 and within the category of awareness of pressure without pain (scores 1–2). Similarly, none of the subsequent publication/abstract has reported pain during the insertion, treatment, or removal of the device.

DISCUSSION

In total, 31 articles/abstracts (five clinical trials, three case reports, and 23 meeting abstracts) were included and systematically reviewed in this study. The outcomes of all the peer-reviewed reports are

that vectored thermal pulsation therapy is highly effective at restoring meibomian gland function and also reducing dry eye symptoms. In addition, it is effective in improving other downstream correlates of ocular surface health such as TBUT, LLT, ocular surface staining, and, in some cases, osmolarity.

The duration of efficacy of the therapy is still being investigated. Of the reported studies, there were two randomized controlled clinical trials observing the duration of effect in terms of gland function and dry eye symptoms for 6 and 12 months both demonstrating that a single vectored thermal pulsation therapy has the potential to remain effective for up to 12 months. Uncontrolled reported case series (up to 4 years following a single treatment) demonstrate that the effects can last significantly longer than 12 months. The results of uncontrolled studies, although thought to be provoking, remain somewhat speculative. In contrast, the results of the two long-term controlled studies are compelling. In both cases, the single LipiFlow treatment was compared with a 3-month 'best medicine/standard of care' whereby a twice-daily regimen of warm compresses and lid hygiene/massage was administered and compliance was closely tracked. These designs controlled for the placebo effect of receiving any therapy (LipiFlow vs. Standard of care) rendering the results directly comparable. In both the cases, the single 12-min vectored thermal pulsation therapy performed better than the twice-daily 'standard-of-care' approach. Furthermore, they demonstrated that the single 12-min therapy was capable of lasting for up to 6–12 months, limited by the length of the trial. In both the trials, the 'standard-of-care' control groups were permitted to cross-over and receive the single 12-min vectored thermal pulsation therapy after 3 months of being compliant with the twice-daily standard-of-care routine.

No single aspect of the lacrimal functional unit operates in isolation. The various moving parts must work together for the ocular surface health to be fully restored. Thus, this review should not be misinterpreted to say that addressing meibomian gland function in isolation is sufficient for full restoration of ocular surface health. However, no other single-dose therapy offers the same efficacy profile for reducing dry eye symptoms, improving meibomian gland function and other correlates of the ocular surface health, as well as vectored thermal pulsation for the evacuation of stagnated gland contents. Arguably, one cannot achieve ocular surface health in the absence of a healthy lipid layer, hence the data leading to the conclusion that MGD is the leading cause of dry eye [3,4].

CONCLUSION

These results gathered from multiple sites on multiple continents all serve to confirm that evacuation of stagnated gland contents remains the necessary core therapy for rehabilitating gland function and reducing symptoms of eye dryness in patients with MGD. This shift in understanding the vital role of meibomian gland function in the maintenance of the ocular surface health and wellness requires that we consider evaluating all of our patients for MGD and that we then manage them appropriately. As with other diseases wherein new metrics and therapies expand our understanding of a disease process, the management of ocular surface dryness has shifted from the focus on tear production and quantity to measures of meibomian gland function and tear film stability.

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Conflicts of interest

C.A.B. is an employee, A.N.C. is a consultant, and D.R.K. is a cofounder and consultant for TearScience, Inc.

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